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# MERCK

Merck KGaA · Darmstadt  
Deutschland

Dockets Management Branch  
(HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061

ROCKVILLE, MARYLAND 20852  
USA

**Docket No. 98D-0994; Draft Guidance for Industry on BACPAC I:  
Intermediates in Drug Substance Synthesis; Bulk Actives Post-approval Changes:  
Chemistry, Manufacturing and Controls (CMC) Documentation;  
Notice of Availability Appearing in the Federal Register of November 30, 1998  
(63FR65793)**

Dear Sir/Madam

Merck KGaA is a manufacturer of active ingredients for drug products since 1827. We supply customers throughout the world including the USA. We have been inspected regularly by the FDA since 1968.

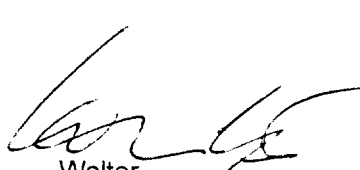
Therefore we are affected by the "Draft Guidance for Industry on BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Post-approval Changes: Chemistry, Manufacturing and Controls (CMC) Documentation".

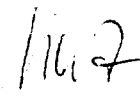
We appreciate very much the opportunity to provide comments on this important draft guidance for industry.

Sincerely,  
Merck KGaA

i.V.

i.A.

  
Walter

  
Dr. Sinz

98D-0994

33120404.doc pl

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## Attachment

### Docket No. 98D-0994; BACPAC I:

#### General Comments

We understand that the changes covered by BACPAC I only encompass changes in the information filed in the approved application.

It should be sufficient to prove the equivalence by comparing three postmodification batches to three recent premodification batches. Equivalence is demonstrated if impurities are within the stated limits of the specification or if not specified at or below the upper statistical limit of historical data. When equivalence is proven before the final intermediate filing the change in an annual report should be sufficient.

All BACPAC I changes should be reported to the FDA and the drug product manufacturer. However the drug product manufacturer should not be obliged to file a CBE supplement or an annual report for such changes, since the drug substance quality is not affected. Furthermore, if an API intermediate manufacturer supplies other API manufacturers or drug product manufacturers it does not make good economic or scientific sense for the FDA to have to assess several NDAs which all reference the same change made by one API manufacturer in one DMF.

Changes made prior to the final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effected supplement is suggested.

#### Specific comments

p. 2, line 17-20

Postapproval changes affecting (1) ~~synthetic peptides~~, (2) oligonucleotides, (3) radio-pharmaceuticals, or (4) drug substances derived exclusively by isolation from natural sources or produced exclusively by procedures involving biotechnology are not addressed in this document.

*Synthetic peptides should be within the scope of BACPAC I as there is no principle difference between peptides and other drug substances produced by organic synthesis.*

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p. 4, line 95-97

~~For example, if the drug substance is a mixture of isomers, then the same quantitative mixture should be obtained after the change.~~

*This sentence should be deleted as it is covered by the general equivalence requirement.*

p. 5, line 123-124

The level of impurities should be assessed by comparing three postmodification batches to ~~three ten~~ premodification ~~commercial~~ batches.

*(see general comments)*

p. 5, line 128-130

The impurity profile will be considered equivalent after a given change if at least three postmodification batches of either an isolated (or in situ, if appropriately justified) intermediate or the drug substance are evaluated and the test data demonstrate that for:

*The demonstration of equivalence may take place at an in situ intermediate if appropriate justification is provided:*

p. 5, line 137-138

Existing impurities, including residual solvents if relevant, ~~are at or below the upper statistical limit of historical data~~ are within the approved specification or, if not specified, are at or below the upper statistical limit of historical data.

p. 5, line 139

Total impurities are within the stated limits, or, if not specified, are at or below the upper statistical limit of historical data.

p. 6, line 149-150

Existing impurities, including organic solvents if relevant, are within the stated limits, or, if not specified, are at or below the upper statistical limit of historical data.

p. 6, line 159

~~In situ intermediates are generally not appropriate for demonstrating equivalence.~~

In situ intermediates, if appropriately specified, should be treated as isolated intermediates.

p. 7, line 200

Conformance to historical ~~particle size distribution profile~~ specification.

p. 8, lines 227-229

Site changes within a single facility or within a contiguous campus that fall within the scope of sections IV.A and IV.A1 need not be filed with the Agency, and equivalence testing as described in this document need not be carried out.

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p. 8, lines 266

~~Changes being effected~~ **Annual Report** supplement if

For changes made prior to the isolated final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effectuated supplement is suggested.

p. 10/11, lines 275-276

Scale changes include increases and decreases in the batch size of the intermediates including the final intermediate in cases where the equipment geometry may have an influence on the reaction.

p. 11, line 330

Specification changes made to comply with compendial changes or adoption of limits of compendia including broadening of the own historical limit.

p. 14, lines 395

~~Changes being effected~~ **Annual report.**

*For changes made prior to the isolated final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effectuated supplement is suggested.*

p. 15, line 442

~~Changes being effected supplement.~~ **Annual report.**

*For changes made prior to the isolated final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effectuated supplement is suggested.*

p. 17, line 480

~~Prior approval supplement.~~ **Annual report.**

*For changes made prior to the isolated final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effectuated supplement is suggested.*

# For all International PowerShip Shipments

## 1 From

Date

Sender's Name

Company

Address

City

Country

Sender's FedEx Account Number

Phone

Dept./Floor

Address

City

Country

State/Province

ZIP/Postal Code

## 2 Your Internal Billing Reference Information

## 3 To

Recipient's Name

Company

Address

City

Country

Phone

Dept./Floor

Address

City

Country

State/Province

ZIP/Postal Code

Recipient's I.D. number for Customs purposes (e.g. IN/VAT/EIN or any locally required)

☐ For HOLD at FedEx Location tick here

☐ For Saturday Delivery tick here (Extra charge may apply. Not available at all locations.)

## 4 Shipment Information

FedEx cannot estimate Customs charges. ALL shipments can be subject to Customs charges.

Total Packages (Shipper's Load and Count/SLAC) Total Weight ☐ lbs. ☐ kgs. ☐ DIM Weight ☐ lbs. ☐ kgs.

Commodity Description	Harmonised Code	Country of Manufacture	Value for Customs
UNION			

Total Declared Value For Carriage Specify Currency Total Value For Customs

☐ For Harmonised Code #'s over U.S. \$2,500 or those which require a U.S. Dept. of Commerce validated Export License, attach a completed Shipper's Export Declaration form and tick here.

If filing by SEC 30.39 FTSR, no SED required, however, fill in CAS or SAS

For U.S. Export Use Only

FedEx Tracking Number 8112 6906 0437 Form I.D. No. 0423

5 Broker Selection 40 ☐ FedEx International Broker Select (Not available to all destinations)

Broker's Name

City/Country/Country

Postal Code

Phone

## 6 Service

Not all services available to all destinations

6 ☐ FedEx Intl. First (Postal code required) (Higher rates apply) 1 ☐ FedEx Intl. Priority 3 ☐ FedEx Intl. Economy (FedEx Letter/Envelope/Pak rate not available) 70 ☐ FedEx Intl. Priority Freight 86 ☐ FedEx Intl. Economy Freight

## 7 Packaging

6 ☐ FedEx Letter/Envelope 2 ☐ FedEx Pak 1 ☐ Other Packaging

## 8 Special Handling

Not all options available to all destinations

Does this shipment contain dangerous goods?\*

(One box must be ticked) ☐ No 4 ☐ Yes (As per attached Shipper's Declaration) 8 ☐ Yes (Shipper's Declaration not required)

☐ Tick here if goods are not in free circulation and provide C.I. (For EU only)

CA ☐ Cargo Aircraft Only

6 ☐ Dry Ice Dry Ice, 9, UN 1845 x kg

## 9 Payment

TRANSPORTATION CHARGES PAID BY:

1 ☐ Sender 2 ☐ Recipient 3 ☐ Third Party 4 ☐ Credit Card 5 ☐ Cash/Cheque (Enter FedEx Account No. or Credit Card No. below) Obtain Recipient/Third Party FedEx Account No.

FedEx Account No. Credit Card No. Exp. Date

DUTIES AND TAXES PAID BY: FedEx cannot estimate Customs charges

1 ☐ Sender 2 ☐ Recipient 3 ☐ Third Party 5 ☐ Cash/Cheque

Total Transportation (Excludes Customs charges)

FedEx Account No. Specify Currency

## 10 Required Signature

By giving us your shipment, you agree to the conditions on the back of this Non-Negotiable Air Waybill. Certain international treaties, including the Warsaw Convention, may apply to this shipment and limit our liability for damage, loss or delay, as described in the Conditions of Contract.

WARNING: These commodities, technology or software were exported from the United States in accordance with the Export Administration Regulations. Diversion contrary to U.S. Law prohibited.

Sender's Signature: Date Executed:

Received above shipment in good order and condition. We agree to pay all charges including Customs duties and taxes as applicable and to the Conditions of Contract as stated on the reverse side of the consignee copy.

Recipient's Signature:

FedEx Courier Receipt: Date: (For Letter of Credit shipments only)

FedEx Tracking Number

8112 6906 0437 0423

Form I.D. No.

Handling Units	Origin Station I.D.	Destination Station I.D.	URSA Routing
Total Volume (cm.)	DE-424	LDON	EM/ED6
Received At: 1 <input type="checkbox"/> Reg. Stop 2 <input type="checkbox"/> On-Call Stop 3 <input type="checkbox"/> Drop Box 4 <input type="checkbox"/> World Service Center 5 <input type="checkbox"/> Station	Forms Attached: <input type="checkbox"/> CI <input type="checkbox"/> SED		
Base Charges	Declared Val. Chrg.	Other	ODA/UPA
FedEx Emp. #	Audit Emp. #	Date	Time
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